Published in final edited form as:

J Am Acad Dermatol. 2011 August ; 65(2): 289–296. doi:10.1016/j.jaad.2010.06.067.

Effectiveness and causes for failure of surveillance of CDKN2A mutated melanoma families

Jasper I. van der Rhee, MD¹, Femke A. de Snoo, MD, PhD^{1,2}, Hans F.A. Vasen, MD, PhD³, Wolter J. Mooi, MD, PhD⁴, Hein Putter, PhD⁵, Nelleke A. Gruis, PhD¹, Nicole A. Kukutsch, MD, PhD^{1,*}, and Wilma Bergman, MD, PhD^{1,*}

¹Department of Dermatology, Leiden University Medical Center, Leiden, the Netherlands ²Human and Clinical Genetics, Leiden University Medical Center, Leiden, the Netherlands ³the Netherlands Foundation for the Detection of Hereditary Tumors, Leiden, the Netherlands

⁴Department of Pathology, VU University Medical Center, Amsterdam, the Netherlands ⁵Medical Statistics, Leiden University Medical Center, Leiden, the Netherlands

Abstract

Background—For over 25 years families with an increased susceptibility to melanoma have been under surveillance at our institution.

Objective—To investigate the effectiveness of surveillance for CDKN2A mutated families and causes for failure of the program in patients with late detected tumours.

Methods—In a retrospective case-control study, Breslow thickness of melanomas diagnosed in relatives enrolled in the surveillance program were compared to melanomas of unscreened index patients. We investigated the influence of mode of detection and length of surveillance interval on outcome.

Results—Surveillance melanomas (n = 226, median thickness: 0.50 mm) had a significantly lower Breslow thickness (multiplication factor: 0.61 (95% CI 0.47 – 0.80), p < 0.001) than index melanomas (n = 40, median thickness: 0.98 mm). Index melanomas were more likely diagnosed with a Breslow thickness > 1.0 mm (Odds ratio: 3.1 (95% CI 1.2 – 8.1), p = 0.022). 53% of surveillance melanomas were diagnosed during regular screens, 7% during patients' first screen, 20% in between regular screens, and 20% in patients who were non-compliant with the surveillance schedule.

The majority of surveillance melanomas (58%) were detected within 6 months after the last screen. There was no correlation between tumour thickness and the length of the screening interval for tumours diagnosed within 24 months since the last screen.

Limitations—The study is retrospective.

© 2010 American Academy of Dermatology, Inc. Published by Mosby, Inc. All rights reserved.

Corresponding author: J.I. van der Rhee, Department of dermatology, B1-Q, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands, Tel: +31 71 5262421, Fax: +31 71 5248106, j.i.van_der_rhee@lumc.nl.

*Contributed equally

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of interest

The authors have no conflict of interest to declare

Conclusions—Surveillance was associated with earlier detection of melanomas. Noncompliance was an important cause for failing surveillance. Shortening surveillance intervals may advance detection of tumours, but may paradoxically not improve prognosis

Keywords

Melanoma; Prevention & Control; Dysplastic nevus syndrome; Genes, CDKN2A

Introduction

About 10% of primary cutaneous malignant melanomas have been reported to occur in families.¹ In 1994, germline mutations in the CDKN2A gene (MIM# 600160) were demonstrated in kindreds with hereditary melanoma.^{2,3} CDKN2A encodes two distinct proteins: p16INK4 and p14ARF, both of which function as tumour suppressors. CDKN2A is the most prevalent high penetrance melanoma susceptibility gene, mutations being detected in the germline in 20–40% of melanoma families.^{4–6} Mutations in CDKN2A have an estimated penetrance of 67% by the age of 80 years.⁴

In 1981 the familial melanoma study group of the Leiden University Medical Center (LUMC) initiated a surveillance program for familial melanoma kindreds. Many of the first families that were screened at the LUMC were later shown to have a founder mutation in CDKN2A, consisting of a 19 base pair deletion in exon 2 (the p16-Leiden mutation).⁷ In 1989 we evaluated the surveillance program for these families, and reported that screen-detected melanomas (n = 31) had more favourable prognostic characteristics than those detected before the start of the surveillance program (n = 19).⁸ We have noticed however that in spite of the surveillance program, some melanomas are detected relatively late. Possible explanations include: noncompliance with follow-up instructions; intervals between screens being too long to warrant early detection in all instances, since some melanomas grow rapidly⁹; failure to recognize melanomas due to an atypical clinical presentation¹⁰ or inadequate screening.

In the current study we compared the Breslow thickness of 226 melanomas of patients from p16-Leiden mutation positive families who were enrolled in the surveillance program with 40 melanomas of index patients from the same families, diagnosed before recognition of heredity for melanoma in these families. In addition we looked at the length of the surveillance intervals and the mode of detection of the melanomas.

Materials and methods

The majority of families under surveillance at the LUMC were ascertained through the Pigmented Lesions Clinic (PLC) of the Department of Dermatology from 1980 onwards. Family trees have been constructed for each kindred, initially at the clinic and later at the Netherlands Foundation for the Detection of Hereditary Tumours (NFDHT). Ascertainment of family data at the clinic¹¹ and the NFDHT^{8,12} have been described in detail elsewhere. Family members of clinically proven melanoma pedigrees were invited to the surveillance program, which consisted of an annual total skin examination. If a melanoma was diagnosed, surveillance was intensified during the first five years after diagnosis (every 3 months during the first year, every 4 months during the second year, and every 6 months during the third to fifth year).

Before and following the identification of the p16-Leiden mutation in 1994, blood samples for research purposes have been collected from relatives who signed an informed consent.

Pedigree information was updated on a regular basis. We consider cancer data for all included families to be complete from 1970 onwards. All melanomas diagnosed in family members that had been enrolled in the LUMC surveillance program were selected. These included tumours detected at the PLC of the LUMC, as well as melanomas incidentally detected at other departments and by general practitioners. Melanomas detected before the start of the surveillance program in relatives that were under surveillance because of previous melanomas were also included. They were all termed surveillance melanomas. Melanomas diagnosed in patients that had continued their surveillance at another institution were excluded. The first melanoma of the first two melanoma patients from each family served as controls. They were detected before recognition of heredity for melanoma in these families, and termed index melanomas. In total 344 melanomas diagnosed in relatives from 37 families were eligible to the study.

For each patient data was collected concerning date of birth and gender. For all melanomas data on Breslow thickness, histological type and date of diagnosis were gathered and the patients' age at time of diagnosis was calculated. Screening intervals were calculated as the time between the last screen and melanoma detection. All tumors with missing data on Breslow thickness or histological type, all in situ melanomas (Mis), and melanomas other than the superficial spreading histological type (n= 132) were reviewed by one of us (WM). Twenty-eight lesions were excluded from the study, because they were reclassified as benign (n = 22), unclassifiable (n = 5), or as recurrent melanoma (n = 1). Mis and invasive melanomas with missing data on Breslow thickness that were unavailable for revision were excluded from the study.

We distinguished four modes of detection after enrolment in the surveillance program and surveillance melanomas were classified accordingly. Melanomas diagnosed at the first screen, were termed first screen melanomas (figure 1, arrow 1). If melanomas were detected at a subsequent screen, they were termed regular screen melanomas (figure 1, arrow 2). Tumours that were detected in between scheduled screens were termed interval melanomas (figure 1, arrow 3). The final category, noncompliance melanomas, consisted of melanomas that were detected more than two months after the recommended screening interval (figure 1, arrow 4). The margin of two months was taken because there have been waiting lists for the PLC in the past.

Statistical analysis

Multivariate linear regression and binary logistic regression analyses were performed to calculate the effect of surveillance on Breslow thickness. Comparisons were made between surveillance melanomas and index melanomas, and between the four surveillance melanomas categories and index melanomas. In the linear regression analyses a log-transformed Breslow thickness was used. Since differences in the log-transformed variable translate to multiplication factors on the original scale, results are reported as multiplication factors on the original scale. In the logistic regression analyses Breslow thickness was analyzed as a categorical variable, coded 1 for Breslow thickness ≤ 1.00 mm, and 2 for > 1.00 mm. All analyses were adjusted for gender, age at diagnosis (in years) and year of diagnosis.

Many patients had multiple primary melanomas. We anticipated that these patients had their subsequent melanomas diagnosed at a more favourable prognostic stage than their first melanoma, not just because of surveillance, but also because of a change of the patients' and physicians' attitudes and behaviour because of the previous (first) melanoma. For this reason we adjusted for melanoma rank, using a covariate coded 1 for first melanoma and 2 for all subsequent melanomas. In addition we used generalized estimating equations (GEE)¹³ to

correct for within-patients correlations; this method uses sandwich estimators to calculate robust standard errors. Correlation between the length of the screening interval and tumour thickness were calculated with linear regression analyses, with log-transformed Breslow thickness as dependent and the screening interval (in years) as covariate.

All analyses were performed with SPSS 14.0 and R 2.5.1. The package geepack14 was used for the calculation of adjusted standard errors. Statistical significance was determined at $\alpha = .05$, and all tests were two-sided. For analyses in which more than two groups were compared a Bonferroni correction for multiple testing was performed.

Results

In total, 266 melanomas from 114 patients were included (table 1). These melanomas consisted of 40 index melanomas and 226 surveillance melanomas. Median Breslow thickness was 0.98 mm for index melanomas and 0.50 mm for surveillance melanomas (table 2). The mean thickness of surveillance melanomas was 0.61 times that of index melanomas (95% confidence interval (95% CI): 0.47 – 0.80, $p < 0.001$). The probability of being diagnosed with a Breslow thickness >1.00 mm was significantly larger for index melanomas (OR: 3.1, CI: 1.2 – 8.1, $p = 0.022$).

Mode of detection of surveillance melanomas

Classification according to mode of detection was possible for 191 surveillance melanomas (85%, table 2). Tumours were classified as follows; 13 first screen (7%), 102 regular screen (53%), 38 interval (20%) and 38 noncompliance melanomas (20%). Compliance was related to the number of melanomas patients had previously been diagnosed with. The proportion of noncompliance melanomas was as high as 46% among first melanomas, and only 26% of first melanomas were regular screen melanomas. For subsequent melanomas patients' compliance steadily increased (table 2).

Screening interval

Most regular screen (72%) and interval (68%) melanomas were diagnosed in patients that were under intensified surveillance because of a previous melanoma. The median interval between the last screen and moment of detection was 5 months for regular screen melanomas, 3.5 months for interval melanomas and 24 months for noncompliance melanomas (table 2). The Breslow thickness of surveillance melanomas was not correlated with the length of the screening interval for intervals less than 24 months (table 3, linear regression analysis, multiplication factor: 1.01 / year, 95% CI: 0.83 – 1.23), $p = 0.917$). If melanomas detected after an interval of more than 24 months were included in the analysis a significant correlation between screening interval and Breslow thickness was found (multiplication factor: 1.09 / year, 95% CI: 1.03 – 1.15, $p = 0.003$).

Detection of interval melanomas

Most interval melanomas ($n = 21$, 55%) were detected by patients themselves, with a median thickness of 0.55 mm (range: in situ – 1.60 mm), after a median interval of 5 months (range: 1–11). Ten interval melanomas (26%) were diagnosed by physicians at an appointment for the excision of another pigmented lesion, judged to be suspicious at the last screen (thickness: 0.40 mm (in situ – 0.90 mm), interval: 1 months (0 – 2)). Physicians consulted for another medical condition diagnosed six of the interval melanomas (16%, thickness: 0.38 mm (in situ – 3.90 mm), interval: 7.5 months (2 – 11)). One interval melanoma was detected in a research project (thickness: 2.00 mm, interval 3 months).

Tumour thickness according to mode of detection

The tumour thickness according to mode of detection is shown in table 4. Regular screen melanomas were significantly thinner than index melanomas Multiplication factor: 0.53, 95% CI 0.46 – 0.87, $p < 0.001$) and at borderline significance, first screen melanomas were thinner than index melanomas Multiplication factor: 0.63, 95% CI 0.46 – 0.87, $p = 0.0053$, significance at $\alpha = .005$, because of multiple testing, table 5). The probability of diagnosing a tumour with Breslow thickness > 1.00 mm was not significantly different between any of the screening categories and index melanomas (table 5). To further investigate possible differences between the different screening categories we performed a sub-analysis with a cut-off point of 0.75 mm, as used in older versions of the AJCC staging system. The probability of being diagnosed with a tumour thickness > 0.75 mm was significantly larger for index melanomas than for regular screen melanomas (OR 14.6, CI: 4.4 – 48.2, $p < 0.001$, table 5), interval melanomas (OR 7.7, CI: 2.0 – 29.3, $p = 0.0029$) and first screen melanomas (OR 6.6, 95% CI 1.8 – 24.4, $p = 0.0047$). Noncompliance melanomas had a higher probability of being diagnosed with a Breslow thickness > 0.75 mm than regular screen melanomas (OR 4.8, CI: 1.8–13.2, $p = 0.0021$).

Discussion

We evaluated the effectiveness of our surveillance program for familial melanoma kindred with the p16-Leiden mutation in CDKN2A. The tumour thickness of 226 melanomas of relatives enrolled in the surveillance program was compared with 40 melanomas diagnosed in index patients.

Surveillance melanomas were significantly thinner than index melanomas, indicating that melanomas were detected in an earlier stage during the surveillance program. This is to some degree surprising, given the fact that only 53% of the surveillance melanomas were detected at a regular screen. Seven percent of surveillance melanomas were detected at first screens, 20% in between regular screens, and 20% were detected in patients that were not compliant with follow-up instructions at the time of diagnosis. Mode of ascertainment clearly influenced the effectiveness of surveillance. Only first screen and regular screen melanomas had a significantly lower Breslow thickness than index melanomas. There were no significant differences in the probability of being diagnosed with a tumour thickness > 1.00 mm between melanomas of any of the four surveillance melanomas categories and index melanomas. It is likely that this was due to lack of statistical power, as significance was determined at $\alpha = .005$ because of multiple testing. In a sub-analysis with a cut-off point of 0.75 mm, all surveillance melanomas categories except for noncompliance melanomas were associated with a significantly smaller probability of being diagnosed with a tumour thickness > 0.75 mm compared with index melanomas.

The mean tumour thickness of regular screen melanomas (0.58 mm) was comparable to those of screen detected melanomas reported in other studies (0.52 mm – 0.56 mm).^{8,15,16} Hansson et al. reported that 93% of 41 melanomas detected in the Swedish national preventive program for melanoma kindred had a tumour thickness < 1.00 mm¹⁷, which was similar to the 94% in our study. These other studies did not specify however whether interval melanomas and melanomas in non-compliant patients were included.

First-screen melanomas had a higher mean tumour thickness than regular screen melanomas, but the difference was not statistically significant. First-screen melanomas did have a significantly lower Breslow thickness than index melanomas however. These findings are in accordance with earlier studies.^{8,15,16}

As much as one fifth of melanomas were diagnosed in patients that were not compliant with follow-up instructions at the time of diagnosis. Moreover almost half of patients were non-compliant at the time of diagnosis of their first melanoma. Noncompliance had a negative impact on melanoma detection as the probability of being diagnosed with a Breslow thickness > 0.75 mm was significantly greater for noncompliance melanomas compared with regular screen melanomas (OR 4.8). Noncompliance has previously been reported to be a frequent problem in the follow-up of patients with a primary melanoma¹⁸, and in the long-term (dermoscopic) follow-up of patients with atypical pigmented lesions^{19,20} as well.

A considerable proportion of melanomas (20%) was diagnosed in between scheduled screens. The majority of these interval melanomas was detected by patients themselves after a median interval of five months since the last screen. The Breslow thickness of interval melanomas was comparable to that of regular screen melanomas. This was probably facilitated by the fact that participants of the surveillance program were repeatedly educated about the characteristics of melanoma and instructed to perform regular skin self-examinations and promptly return to the clinic in case of symptomatic, changing or new fast growing lesions.

The large number of interval melanomas raises the question whether the standard screening interval of our surveillance program (12 months) is adequate. In this study the median screening interval of regular screen melanomas was 5 months, because most tumours were diagnosed in patients that were under intensified surveillance because of a previous melanoma. Our results suggest that the majority of melanomas became detectable within six months after the preceding screen. Paradoxically we found that tumour thickness was not correlated with the length of the screening interval for intervals less than 24 months. This may have been due to self-selection bias however, as patients with a worrisome lesion are more likely to return to the clinic before the scheduled screen (interval melanomas) and are less likely to be non-compliant with follow-up instructions. It may also indicate that health-education or increased awareness due to earlier melanomas enabled patients to determine themselves when to return. Alternatively this finding could be explained by the growth-pattern of melanomas. It has been postulated that most melanomas (except for nodular melanomas) initially only exhibit radial expansion, without substantial vertical expansion.²¹ Based on this theory it could be argued that melanomas can be detectable for a long time, before a substantial increase in their Breslow thickness occurs.

Our study had a retrospective design and as a consequence classification of melanomas into different screening categories was dependent on completeness of data in patient charts. To limit the number of misclassifications we were very restrictive in categorizing doubtful cases and therefore 15% of surveillance melanomas were not further categorized. Our results suggest a number of ways to improve the surveillance program. First, it is potentially very rewarding to increase efforts to improve patients' compliance with follow-up instructions. Second, early detection of clinically atypical and fast-growing melanomas may be promoted by instructing patients to report to the clinic in case of any changing or new (fast growing) lesion. As a final point, we believe it is debatable whether our standard screening interval should be shortened from 12 to 6 months. On the one hand the majority of melanomas seemed to be detectable within six months after the preceding screen, so a shorter interval would advance melanoma detection. In addition compliance with follow-up instructions may improve with shorter screening intervals.²² On the other hand it is unknown whether shortening of the screening interval would result in detection of tumours in a more favourable stage.²³ Moreover adequate health education, and promotion of skin self-examination may be a more cost-effective alternative than decreasing the screening interval. Further studies will be required to answer these questions.

Acknowledgments

We would like to acknowledge Clasine van der Drift for her assistance in collecting data at the Netherlands Foundation for the Detection of Hereditary Tumors.

Funding

This research was supported by the National Cancer Institute (NCI) of the US National Institutes of Health (NIH), contract number CA83115)

Abbreviations

LUMC	Leiden University Medical Center
PLC	pigmented lesions clinic
Mis	Melanoma in situ

Reference List

1. Ang CG, Kelly JW, Fritschi L, Dowling JP. Characteristics of familial and non-familial melanoma in Australia. *Melanoma Res.* 1998; 8:459–464. [PubMed: 9835460]
2. Hussussian CJ, Struewing JP, Goldstein AM, Higgins PA, Ally DS, Sheahan MD, et al. Germline p16 mutations in familial melanoma. *Nat.Genet.* 1994; 8:15–21. [PubMed: 7987387]
3. Kamb A, Gruis NA, Weaver-Feldhaus J, Liu Q, Harshman K, Tavtigian SV, et al. A cell cycle regulator potentially involved in genesis of many tumor types. *Science.* 1994; 264:436–440. [PubMed: 8153634]
4. Bishop DT, Demenais F, Goldstein AM, Bergman W, Bishop JN, Bressac-de Paillerets B, et al. Geographical variation in the penetrance of CDKN2A mutations for melanoma. *J.Natl.Cancer Inst.* 2002; 94:894–903. [PubMed: 12072543]
5. de Vries E, Houterman S, Janssen-Heijnen ML, Nijsten T, van de Schans SA, Eggermont AM, et al. Up-to-date survival estimates and historical trends of cutaneous malignant melanoma in the south-east of The Netherlands. *Ann.Oncol.* 2007; 18:1110–1116. [PubMed: 17434898]
6. Goldstein AM, Chan M, Harland M, Hayward NK, Demenais F, Bishop DT, et al. Features associated with germline CDKN2A mutations: a GenoMEL study of melanoma-prone families from three continents. *J.Med.Genet.* 2007; 44:99–106. [PubMed: 16905682]
7. Gruis NA, van der Velden PA, Sandkuijl LA, Prins DE, Weaver-Feldhaus J, Kamb A, et al. Homozygotes for CDKN2 (p16) germline mutation in Dutch familial melanoma kindreds. *Nat.Genet.* 1995; 10:351–353. [PubMed: 7670475]
8. Vasen HF, Bergman W, van Haeringen A, Scheffer E, van Slooten EA. The familial dysplastic nevus syndrome. Natural history and the impact of screening on prognosis. A study of nine families in the Netherlands. *Eur.J.Cancer Clin.Oncol.* 1989; 25:337–341. [PubMed: 2702987]
9. Liu W, Dowling JP, Murray WK, McArthur GA, Thompson JF, Wolfe R, et al. Rate of growth in melanomas: characteristics and associations of rapidly growing melanomas. *Arch.Dermatol.* 2006; 142:1551–1558. [PubMed: 17178980]
10. Koch SE, Lange JR. Amelanotic melanoma: the great masquerader. *J.Am.Acad.Dermatol.* 2000; 42:731–734. [PubMed: 10775846]
11. de Snoo FA, Bishop DT, Bergman W, van LI, van der DC, van Nieuwpoort FA, et al. Increased Risk of Cancer Other Than Melanoma in CDKN2A Founder Mutation (p16-Leiden)-Positive Melanoma Families. *Clin.Cancer Res.* 2008; 14:7151–7157. [PubMed: 18981015]
12. Vasen HF, Gruis NA, Frants RR, Der Velden PA, Hille ET, Bergman W. Risk of developing pancreatic cancer in families with familial atypical multiple mole melanoma associated with a specific 19 deletion of p16 (p16-Leiden). *Int.J.Cancer.* 2000; 87:809–811. [PubMed: 10956390]
13. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics.* 1986; 42:121–130. [PubMed: 3719049]

14. Højsgaard S, Halekoh U, Yan J. The R Package geepack for Generalized Estimating Equations. *Journal of Statistical Software*. 2005; 15:1–11.
15. Masri GD, Clark WH Jr, Guerry D, Halpern A, Thompson CJ, Elder DE. Screening and surveillance of patients at high risk for malignant melanoma result in detection of earlier disease. *J.Am.Acad.Dermatol*. 1990; 22:1042–1048. [PubMed: 2370329]
16. Carey WP Jr, Thompson CJ, Synnestvedt M, Guerry D, Halpern A, Schultz D, et al. Dysplastic nevi as a melanoma risk factor in patients with familial melanoma. *Cancer*. 1994; 74:3118–3125. [PubMed: 7982177]
17. Hansson J, Bergenmar M, Hofer PA, Lundell G, Mansson-Brahme E, Ringborg U, et al. Monitoring of kindreds with hereditary predisposition for cutaneous melanoma and dysplastic nevus syndrome: results of a Swedish preventive program. *J.Clin.Oncol*. 2007; 25:2819–2824. [PubMed: 17602087]
18. Kittler H, Weitzdorfer R, Pehamberger H, Wolff K, Binder M. Compliance with follow-up and prognosis among patients with thin melanomas. *Eur.J.Cancer*. 2001; 37:1504–1509. [PubMed: 11506957]
19. Argenziano G, Mordente I, Ferrara G, Sgambato A, Annese P, Zalaudek I. Dermoscopic monitoring of melanocytic skin lesions: clinical outcome and patient compliance vary according to follow-up protocols. *Br.J.Dermatol*. 2008; 159:331–336. [PubMed: 18510663]
20. Schiffner R, Schiffner-Rohe J, Landthaler M, Stolz W. Long-term dermoscopic follow-up of melanocytic naevi: clinical outcome and patient compliance. *Br.J.Dermatol*. 2003; 149:79–86. [PubMed: 12890198]
21. Clark WH Jr, Elder DE, Guerry D, Epstein MN, Greene MH, Van Horn M. A study of tumor progression: the precursor lesions of superficial spreading and nodular melanoma. *Hum.Pathol*. 1984; 15:1147–1165. [PubMed: 6500548]
22. Argenziano G, Mordente I, Ferrara G, Sgambato A, Annese P, Zalaudek I. Dermoscopic monitoring of melanocytic skin lesions: clinical outcome and patient compliance vary according to follow-up protocols. *Br.J.Dermatol*. 2008; 159:331–336. [PubMed: 18510663]
23. Richard MA, Grob JJ, Avril MF, Delaunay M, Thirion X, Wolkenstein P, et al. Melanoma and tumor thickness - Challenges of early diagnosis. *Archives of Dermatology*. 1999; 135:269–274. [PubMed: 10086447]

Figure 1. Screening categories according to mode of ascertainment

Bold vertical lines represent scheduled screening appointment, dashed vertical line represents skipped screening appointment. Arrows indicate the moment of diagnosis, and accompanying numbers refer to the screening category, 1 = 1st screening melanoma, 2 = regular screening melanoma, 3 = interval melanoma, 4 = noncompliance melanoma

Table 1

patient characteristics

Patients		
(n = 114)		
Gender		
Male	50	(44%)
Female	64	(56%)
Number of melanomas/patient		
1	61	(54%)
2	22	(19%)
3–5	19	(17%)
6–10	8	(7%)
> 10	4	(4%)

Table 2

Tumor characteristics according to screening category

	Index	Surveillance				
		First	Regular	Interval	Non-compl.	Unclassified
Patients (n)	35	12	49	20	36	20
Melanomas (n)	40	13	102	38	38	35
Age at diagnosis**						
1 st melanoma (years)	42 (17 – 62)	32 (22 – 72)	34 (15 – 66)	33 (27 – 44)	39 (23 – 67)	27 (15 – 43)
all melanomas (years)	idem	39 (22 – 72)	46 (22 – 72)	35 (25 – 76)	42 (23 – 67)	43 (15 – 64)
Year of diagnosis**						
	'84 ('68 – '00)	'85 ('81 – '04)	'97 ('73 – '06)	'98 ('72 – '06)	'98 ('84 – '06)	'92 ('77 – '06)
Screening interval (months)**						
	NA	NA	5.0 (1 – 14)	3.5 (0 – 11)	24 (12 – 159)	NA
Diagnosis < 5 yrs after previous melanoma						
	NA	NA	73 (71.6%)	26 (68.4%)	4 (10.5%)	NA
Melanoma rank						
1 st melanoma	40	11 (18%)	16 (26%)	6 (10%)	28 (46%)	10
2 nd melanoma	0	2 (6%)	19 (58%)	8 (24%)	4 (12%)	10
3 rd melanoma	0	0	15 (63%)	6 (25%)	3 (13%)	5
> 3 rd melanoma	0	0	52 (71%)	18 (25%)	3 (4%)	10
Breslow thickness						
Median	0.98 mm	0.69 mm	0.50 mm	0.49 mm	0.52 mm	0.50 mm
Range	(0.30 – 12.00)	(0.30 – 1.80)	(Mis – 2.10)	(Mis – 3.90)	(Mis – 2.60)	(Mis – 3.10)
Mean***	1.48 mm	0.75 mm	0.58 mm	0.76 mm	0.84 mm	0.70 mm
						0.68 mm

* Numbers in row don't add up to 92 as some patients with multiple melanomas had melanomas belonging to different screening categories;

** Numbers in table represent median and range; NA, not applicable; Mis, melanoma in situ;

*** based on invasive melanomas only

Table 3

Tumor thickness according to the time interval between the last screening and the moment of melanoma diagnosis

Time Interval	n	Median * (range)	n	Mean ** (SD)
0 – 4 months	69	0.48 (Mis – 2.10)	57	0.62 (0.39)
5 – 8 months	43	0.55 (Mis – 3.90)	36	0.70 (0.64)
9 – 12 months	27	0.50 (Mis – 1.40)	23	0.53 (0.25)
13 – 18 months	11	0.50 (Mis – 1.20)	8	0.68 (0.27)
19 – 24 months	10	0.49 (Mis – 1.00)	8	0.61 (0.28)
> 24 months	17	0.48 (Mis – 2.60)	13	1.07 (0.77)
Total	177***	0.50 (Mis – 3.90)	145	0.67 (0.49)

* based on in situ and invasive melanomas; 95% CI, 95% confidence interval;

** based on invasive melanomas only; SD, standard deviation; Mis, melanoma in situ;

*** one missing value for a noncompliance melanoma.

Table 4

Cumulative number and proportion of cases according to Breslow thickness

Category	Breslow thickness					Total
	Mis	≤ 0.75mm	≤ 1.00mm	≤ 2.00mm	≤ 4.00mm	
Index:	0 (0%)	13 (33%)	23 (58%)	32 (80%)	38 (95%)	40
Surveillance:						
- First screening	0 (0%)	10 (77%)	11 (85%)	13 (100%)	-	13
- Regular screening	17 (17%)	88 (86%)	96 (94%)	101 (99%)	102 (100%)	102
- Interval	8 (21%)	30 (79%)	33 (87%)	37 (97%)	38 (100%)	38
- Noncompliance	7 (18%)	24 (63%)	31 (82%)	36 (95%)	38 (100%)	38
- Not categorized	3 (9%)	29 (83%)	30 (86%)	33 (94%)	35 (100%)	35
Surveillance (all):	35 (16%)	181 (80%)	201 (89%)	220 (97%)	226 (100%)	226

Mis, melanoma in situ

Table 5

Linear and logistic regression analyses

	Linear regression				Logistic regression			
	MF	95% CI	p [*]		OR	95% CI	p [*]	
Covariate								
Screening category								
Index melanomas	1.0	-	-		1.0	-	-	-
First screen	0.63	(0.46 – 0.87)	0.0053		3.4	(0.7 – 16.0)	0.12	(1.8 – 24.4)
Regular screen	0.53	(0.40 – 0.70)	<0.001 ^{\$}		5.7	(1.2 – 28.2)	0.031	(4.4 – 48.2)
Interval	0.65	(0.44 – 0.96)	0.030		2.1	(0.4 – 11.6)	0.40	(2.0 – 29.3)
Noncompliance	0.69	(0.50 – 0.97)	0.031		2.1	(0.6 – 7.2)	0.27	(1.1 – 8.7)
Gender								
Male	1.0				1.0	-	-	-
Female	0.86	(0.73 – 1.01)	0.060		1.3	(0.6 – 2.8)	0.54	(1.0 – 3.1)
Age per 10 years	1.05	(1.00 – 1.11)	0.052		0.84	(0.60 – 1.18)	0.32	(0.75 – 1.10)
Date of diagnosis per 10 years	0.98	(0.88 – 1.09)	0.68		1.32	(0.79 – 2.23)	0.29	(0.85 – 1.72)
Melanoma rank								
Subsequent	1.0				1.0	-	-	-
First	0.93	(0.74 – 1.17)	0.56		1.7	(0.5 – 6.5)	0.43	(0.3 – 2.0)
								0.56

MF, multiplication factor; OR, odds ratio; 95% CI, 95% confidence interval.

^{*} significance level at $p < 0.005$ because of Bonferroni correction;^{\$} statistically significant